Appln. No. 10/674,228
Reply to Office action of August 7, 2006
Response dated December 7, 2006

REMARKS

This is in response to the office action mailed Augustin the above identified application. Applicants request a one month extension of time for response and enclose the required fee.

The Examiner has objected to the specification for the following reasons: The abstract has too many words and that the identifying data for all prior applications should be provided.

In response, applicants provide a substitute abstract which conforms to the word count limitation. Applicants have also amended the specification to insert the identifying data for the application from which the present case claims priority or benefit. The amendments do not constitute new matter. In view of these comments, Applicants believe that the objections to the specification have been obviated.

Claims 1-4 are pending in this application. Claim 1 has been amended to recite the transition language "consisting of" for the method to emphasize that he claimed method requires only the use of two-dimensional electrophoresis to separate extracted cellular proteins, to the exclusion of other methods of separation, e.g. one-dimensional electrophoresis, or a step where the proteins are subjected to a first separation step and, then, subsequently subjected to two-dimensional electrophoresis for further separation/characterization. This amendment does not constitute new matter, since the specification is clear that only two-dimensional electrophoresis is contemplated by the inventors for separating the cellular proteins to which autoantibodies bind.

Claim 3 has been rejected under 35 USC§112,¶1 as lacking enablement for the use of cells from a continuous cell line representative of the patient's tumor in the method of Claim 1, which the Examiner notes is enabled. The Examiner is objecting to "representative" cell lines and cites to numerous (but old) references to support his argument that continuous cell lines are not "representative" of a patient's tumor. The Examiner argues that it would require undue experimentation to identify such cell lines. None of the references cited by the Examiner are close in time to the effective filing date of the application – indeed they predate the application by at least 10 - 15 years. However, contrary to the Examiner's allegations, much has been learned about cell culture in the interviewing time, with numerous cell lines having been developed as surrogates for particular tumors in experimental studies.

Applicants disagree with the Examiner's conclusion. Applicants have provided our example in the specification of a cell line (SY5Y) which is representative of a certain type of tumor – neuroblastoma.

Moreover, the Examiner has explicitly acknowledged the existence of representative cell lines as a surrogate for a patient's tumor, in citing the 1988 paper of Hirsch et al. as anticipating the present invention. While disagreeing with that conclusion, (that the present invention is anticipated). Applicants wish to point out that the Hirsch experiments utilize the L428 cell line as representative of Hodgkins disease tumor cells. As clearly acknowledged by the Examiner in the Office Action, this cell line was first published in 1980 whilst the work of Hirsch et al. was published in 1988. It is furthermore clearly stated by Schaadt et al. that the L428 cell line "...is identical with

that of freshly obtained Hodgkin (H)-and Sternberg-Reed (SR)- cells, except for lack of Cig in the in vitro cells, which is explained by the culture conditions. These finds suggest that the L428 and L439 cell lines are indeed derived from H- and SR- cells ..."(emphasis added). The Examiner adds that these cultured cell lines "are derived from "Hodgkin's disease."

In addition, the inventors also set out in the Specification as filed that "it is also not necessary to utilize primary tissues; cells grown in culture may provide appropriate substitutes for tumor issues or controls" (p8 lines 12114). In identifying proteins to which patients with a tumor produce a specific autoantibody response the source of the proteins is not limiting. The specificity of the reaction is driven by the antibodies present in the sera, and in the ability to demonstrate a lack of antibodies with the same reactivity in the sera of patients without the tumor. The inventors provide further guidance on the above on page 7 (lines 5-28) including "The present invention is based on the discovery that serum from an individual that contains autoantibodies, such as a patient with cancer of the lung or neuroblastoma, can be used to identify protein antigens expressed in cells of a particular tissue, such as, for example, cells, of a tumor, or in a representative cell type, to which the patient has autoantibodies."

Thus, those of skill in the art would not consider it undue experimentation to identify representative cell lines. The invention requires the use of proteins prepared from sources that are either directly related to a tumor, or are derived from the same tissue type, or are cells cultivated from a tumor of the same type. It is abundantly clear from the specification that the protein source does not need to be a tumor, or that it

should be of the same characteristic (i.e., identical) to the tumor. Consequently, the Examiner's interpretation of the example of the discovery of neuroblastoma antigens using the SY5Y cell line as not being commensurate with the scope of the claims is contrary.

For the reasons provided above, applicants maintain that the practice of Claim 3 does not constitute undue experimentation and, thus, is enabled.

Claims 1-4 have been rejected under 35 USC§ 112¶ 1 as lacking an adequate written description, i.e., the inventors are not in possession of the claimed invention.

As noted above, Applicants have amended claim 1 to recite that the method is "consisting of" the recited steps. This amendment is being made to clarify exactly what the claimed invention is – the method is limited to using a two dimensional electrophoresit separation of proteins extracted from a patient's tumor (or a cell line representative of that tumor) and incubating the separated proteins (blotted onto a membrane) with patient sera and with control sera to identify autoantibodies in the cancer patient sera.

Applicants are clearly in possession of this claimed method, which is the only one described in the specification and examples. Applicants have limited the scope of the claim to avoid any extra steps in the method, such as one-dimensional electrophoresis to separate proteins by size or change. The examples specifically provide that lung and neuroblastoma proteins were separated by two dimensional electrophoresis after extraction from cells, blotted and probed with patient and normal sera to identify autoantibodies, which were found.

In view of the amendments and arguments herein, Applicants maintain that they are in possession of the invention as presently claimed and request that the written description rejection be withdrawn.

Claims 1-4 have been rejected under 35 USC § 102(b) as anticipated by Hirsch et al. As noted above, Claim 1 has been amended to limit the claimed method to the use of only two dimensional electrophoretic separation of proteins from a patient's tumor, blotting the separated proteins onto a membrane and incubating the separated proteins with sera from the patient and a control to detect a patient's autoantibodies to the tumor proteins. The method, as presently claimed, excludes other means to separate the tumor proteins other than the 2D electrophoresis, followed by Western blotting.

Applicants maintain (as in prior responses) that Hirsch is inapplicable to the present invention and that the Examiner's interpretation of Hirsch et al. is in error.

In the first part of the study reported by Hirsch et al., lysates of a lymphoblastoid cell line were separated by one-dimensional SDS-PAGE prior to transfer onto a nitrocellulose membrane. The membrane was then cut into strips to allow multiple antisera to be tested in parallel. In this phase of the study, 152 sera from cancer patients and 35 sera from normal controls were used for the one-dimensional Western blotting procedure. Interestingly, the sera appeared to contain either no reactive antibodies or, in a limited number of cases, antibodies against a singe protein species designed p-65. Such antibody response was only seen in 17% of cancer patients (26 of 152) and was also seen in approximately 3% of normal controls.

Having identified those patients exhibiting an autoantibody response against P-65 and those controls lacking such an antibody by 1D Western blotting, Hirsch et al., proceeded to further characterize (but not identify) the P-65 protein by 2D Western blot against sera previously found to have autoantibodies to P-65. Interestingly the representative 2D Western blots of patient and control sera in Hirsch et al. show multiple protein reactivities other than those correlating with P-65 which Hirsch et al. discount as being "the usual background (p205, col.1, line 19).

Thus taken as a whole Hirsh et al. fail to teach:

1. Identification of a protein to which only patients with cancer show an autoimmune response – one control patient had antibodies against P-65.

2. Identification of proteins to which patients with cancer raise an antibody response by performing 2D Western blot and comparing proteins to which antibodies in sera from patients with cancer react, whereas patients without cancer do not – the 2D analysis of Hirsch et al. used a pre-selected P-65 reactive patient (one of only 17% of the cancer group) and a known non-reactive control serum (See page 205, column 1, lines 13-15).

3. Hirsch et al. teach one of ordinary skill in the art away from the current invention by ignoring the multiple spots in the 2DE Western blots of patients (fig 1A) and normal controls (fig 3A) which are dismissed as being "the usual background". Instead, Hirsch et al. teach that prior screening of sera using 1DE for discovery of autoantigens is necessary prior to 2D Western blotting.

Thus, in view of the amendments to the claims and Hirsch et al.'s failure to teach the specifically claimed intervention, the reference does not anticipate the presently claimed invention.

Claims 1-4 have been rejected under 35 USC§104(a) as obvious in view of Hirsch et al., in combination with Krska et al. as set forth above (and as admitted by the Examiner int eh Office Action at page 12, lines 16-17), Hirsch et al. fail to teach the claimed invention. Krska et al. fail to add anything to the teachings of Hirsch et al. to render the calimed invention obvious.

Krska et al merely describe a routine experiment to characterize a bacterial protein using monoclonal antibodies specific for the protein of interest. As such, it contributes no more than the investor's own guidance as to the state of the art of 2D electrophores and Western blotting in the present specification. That Krska discloses a method of 2D Western blotting is not disputed, however it does not use a "signal-generating component bound to an antibody that is specific for antibodies in the subject's sample" (emphasis added) of currently pending claim 4. Krska does not use antibodies specific for antibodies raised against an antigen extracted from a tumor cell or a tumor-derived cell line. Instead, they are detecting a hyperimmune monoclonal antibody raised through immunization with a purified bacterial protein. As such, Krska et al. is totally unrelated to the art of the current invention and is inappropriately combined with Hirsch et al.

Thus, there is no teacings or suggestion to combine Hirsch et al. and Krska et al. to arrive at the presently claimed invention. In view of the amendments to the claims and remarks herein, Applicants maintain that the rejection under 35USC§ 103(a) be withdrawn.

Applicants have requested a one-month extension of time. The Commissioner is hereby authorized to charge the extension fee and any additional payment, or credit any overpayment, to Deposit Account No. 01-2300, **referencing Docket Number 108140.00015.**

Respectfully submitted,

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FEE CALCULATION

Any additional fee required has been calculated as follows:

X If checked, "Small Entity" status is claimed.

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT	(Column 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADD'L FEE	OR	LARGE ENTITY RATE	LARGE ENTITY ADD'L FEE
TOTAL CLAIMS	4 MINUS	21	= 0	x $25	$0.00		x $50	$
INDEP CLAIMS	1 MINUS	3	= 0	x $100	$0.00		x $200	$
☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				+ $180	$0.00	OR	+ $360	$
					$0.00			$

The U.S. Patent and Trademark Office is hereby authorized to charge the current fees and any deficiency or credit any overpayment of fees associated with this communication to Deposit Account No. **01-2300** referencing docket number **108140.00015**.